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Abstract: Background: The pathogenesis and etiology of thoracic aortic aneurysms (TAA) are largely unknown. Preliminary data from patients with aortic dissection and abdominal aneurysms suggest a causal link of obstructive sleep apnea (OSA) on aortic disease. Objectives: The aim of the study was to assess the prevalence of OSA in patients with TAA compared to a matched control group. Method: In this prospective parallel-cohort study, we 2-to-1 matched 208 patients with verified TAA (at the aortic sinus and/or ascending aorta) to 104 controls without TAA according to sex, age, height, weight, and left ventricular ejection fraction. All participants underwent an ultrasound of the thoracic aorta and a level III respiratory polygraphy. OSA was defined as apnea-hypopnea index $\geq 5/h$. The prevalence of OSA was compared with conditional logistic regression and controlling for the matching variables. Results: A total of 312 patients (mean age 65 ± 11 years, 82% male, mean body mass index 27 ± 4 kg/m²) were successfully 2-to-1 matched in the final model. Prevalence of OSA was significantly higher in the TAA-group when compared to the matched control group (63 vs. 47%; odds ratio 1.87 [95% CI 1.05–3.34]; $p = 0.03$). When applying a higher apnea-hypopnea index threshold ($\geq 15/h$), the odds ratio increased to 3.25 (95% CI 1.65–6.42; $p < 0.001$). The median apnea-hypopnea index was higher in patients with TAA (9.2/h [3.3–20.0] vs. 4.5/h [2.2–11.1], $p < 0.001$). Conclusions: Patients with TAA have a higher prevalence of OSA when compared to the general population. Since OSA is effectively treatable and might contribute to the pathogenesis of TAA, further longitudinal trials are needed to assess the association between OSA and TAA.

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Prevalence of Obstructive Sleep Apnea in Patients with Thoracic Aortic Aneurysm: A Prospective, Parallel Cohort Study

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Keywords

Thoracic aortic aneurysm · Epidemiology · Prevalence · Obstructive sleep apnea

Abstract

Background: The pathogenesis and etiology of thoracic aortic aneurysms (TAA) are largely unknown. Preliminary data from patients with aortic dissection and abdominal aneurysms suggest a causal link of obstructive sleep apnea (OSA) on aortic disease. **Objectives:** The aim of the study was to assess the prevalence of OSA in patients with TAA compared to a matched control group. **Method:** In this prospective parallel-cohort study, we 2-to-1 matched 208 patients with verified TAA (at the aortic sinus and/or ascending aorta) to 104 controls without TAA according to sex, age, height, weight, and left ventricular ejection fraction. All participants underwent an ultrasound of the thoracic aorta and a level III respiratory polygraphy. OSA was defined as apnea-hypopnea index $\geq 5/h$. The prevalence of OSA was compared with conditional logistic regression and controlling for the matching variables. **Results:** A total of 312 patients (mean age 65 ± 11 years, 82% male, mean body mass index $27 \pm 4 \text{ kg/m}^2$) were

successfully 2-to-1 matched in the final model. Prevalence of OSA was significantly higher in the TAA-group when compared to the matched control group (63 vs. 47%; odds ratio 1.87 [95% CI 1.05–3.34]; $p = 0.03$). When applying a higher apnea-hypopnea index threshold ($\geq 15/h$), the odds ratio increased to 3.25 (95% CI 1.65–6.42; $p < 0.001$). The median apnea-hypopnea index was higher in patients with TAA (9.2/h [3.3–20.0] vs. 4.5/h [2.2–11.1], $p < 0.001$). **Conclusions:** Patients with TAA have a higher prevalence of OSA when compared to the general population. Since OSA is effectively treatable and might contribute to the pathogenesis of TAA, further longitudinal trials are needed to assess the association between OSA and TAA.

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Introduction

A thoracic aortic aneurysm (TAA) is a localized dilation of the thoracic aorta with an incidence rate of approximately 10 per 100,000 person-years in both sexes

T.G. and P.B. contributed equally to this work.

[1]. The majority of TAAs are sporadic and occur in association with the classical risk factors for atherosclerosis (i.e., smoking, arterial hypertension, and hypercholesterolemia). Nevertheless, these risk factors alone poorly predict the incidence of TAA [2]. Although clinically silent, TAA is associated with life-threatening complications such as thrombosis, dissection, and rupture. The cumulative 5-year risk of rupture ranges from 15 to 20% and primarily depends on the diameter of the aneurysm [1, 3].

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder, caused by complete or partial obstruction of the upper airway, leading to nocturnal apneas and hypopneas. It is estimated, that at least 20% of males and 10% of females in Western countries are affected by asymptomatic OSA [4, 5]. An extensive body of literature has described OSA as a causal factor in the pathogenesis of vascular dysfunction and arterial hypertension [6–8]. OSA is a treatable medical condition and the most common therapies effectively counteract adverse effects of OSA, such as hypertension [7].

Initially, observational studies in patients with Marfan syndrome (a genetic disorder of the connective tissue) reported that the severity of OSA independently affects the aortic diameter and has an influence on the aortic event-free survival rate [9–11]. Furthermore, several cross-sectional studies in the general population reported that OSA is highly prevalent among patients with abdominal aortic aneurysms [12–14] and dissections [14–20]. Finally, longitudinal data suggest that severe OSA may contribute to a faster aneurysm expansion [13] and that the gold standard therapy for OSA (continuous positive airway pressure therapy) may counteract the adverse effects of OSA on the aneurysm expansion [21].

According to the literature, there seem to be three main mechanisms behind the contribution of OSA to aortic disease: (1) increased nocturnal negative intrathoracic pressure surges leading to stretching of the aorta, consecutively leading to its long-term distension; (2) arousal-induced sympathetic activation with subsequent hypertension; and (3) intermittent hypoxia associated with autonomic nervous system activation and consequently increased oxidative stress [6].

Whether there is an association between OSA and TAA is currently unknown. We have aimed to address this knowledge gap by performing a prospective parallel cohort study in patients with and without TAA.

Methods

Study Design and Participants

The primary outcome was the prevalence of OSA in patients with TAA compared to a matched control group. The secondary outcome was the association of OSA (reflected by the apnea-hypopnea index [AHI]) with thoracic aortic diameter. Patients with TAA were enrolled from an ongoing cohort study (ClinicalTrials.gov Identifier: NCT02204774). Matched controls were recruited from the outpatient clinic of the University Hospital Zurich between January and November 2018. Exclusion criteria for both groups were: (1) age <18 years; (2) continuous positive airway pressure therapy for OSA; (3) diagnosis of central sleep apnea; (4) relevant use of substances significantly modulating the respiratory drive, e.g. therapy with or addiction to morphine derivatives or alcohol; (5) pregnancy; (6) moderate-to-severe aortic regurgitation; and (7) moderate-to-severe aortic stenosis. Presence of TAA was defined as an aortic diameter exceeding the sex-specific cut-offs at the level of the sinus of Valsalva (≥ 39 mm for women, ≥ 44 mm for men) or the ascending aorta (≥ 42 mm for women, ≥ 46 mm for men) [22]. For each two patients from the TAA cohort, one control subject was recruited. The 2-to-1 matching was based on variables identified a priori to be of interest. The caliper distances for continuous variables in each pair did not exceed 25% of the standard deviation of the pooled variable. Matching variables included sex (exact), age (± 5 years), height (± 20 cm), weight (± 20 kg), and left ventricular ejection fraction ($\pm 10\%$).

Respiratory Polygraphy

Every patient underwent a full ambulatory level III respiratory polygraphy (ApneaLink Air; ResMed, San Diego, CA, USA) during the habitual sleep time. The setup was as recommended, and all raw data were reviewed manually by two trained investigators (T.G., P.B.) and scored according to the guidelines by the American Academy of Sleep Medicine recommendations from 2007 (version A) [23]. OSA was defined as an AHI ≥ 5 /h.

Echocardiography

Echocardiographic studies were performed on a cardiovascular ultrasound system (Vivid E9 with XDclear, GE Healthcare, Little Chalfont, UK) with a 3.5-MHz transducer. The diameter of the aortic sinus (defined as the largest diameter at the sinus of Valsalva) and the ascending aorta (at the level of the right pulmonary artery) were measured in the left parasternal long axis window using two-dimensional, guided M-mode echocardiography in end-systole. Every measurement was performed at least three times, and data were averaged by the mean. According to the recommendations by the American Society of Echocardiography, the “leading edge-to-leading edge” technique was applied for all measurements [24]. The left ventricular ejection fraction was calculated according to the biplane Simpson’s method.

Blood Pressure Measurement

Blood pressure and heart rate were measured in triplicate with a standard digital automatic monitor (Omron Healthcare Company, Kyoto, Japan) in the sitting position after a period of rest of 5 min. The average of these three blood pressure measurements was used for further analysis [25].

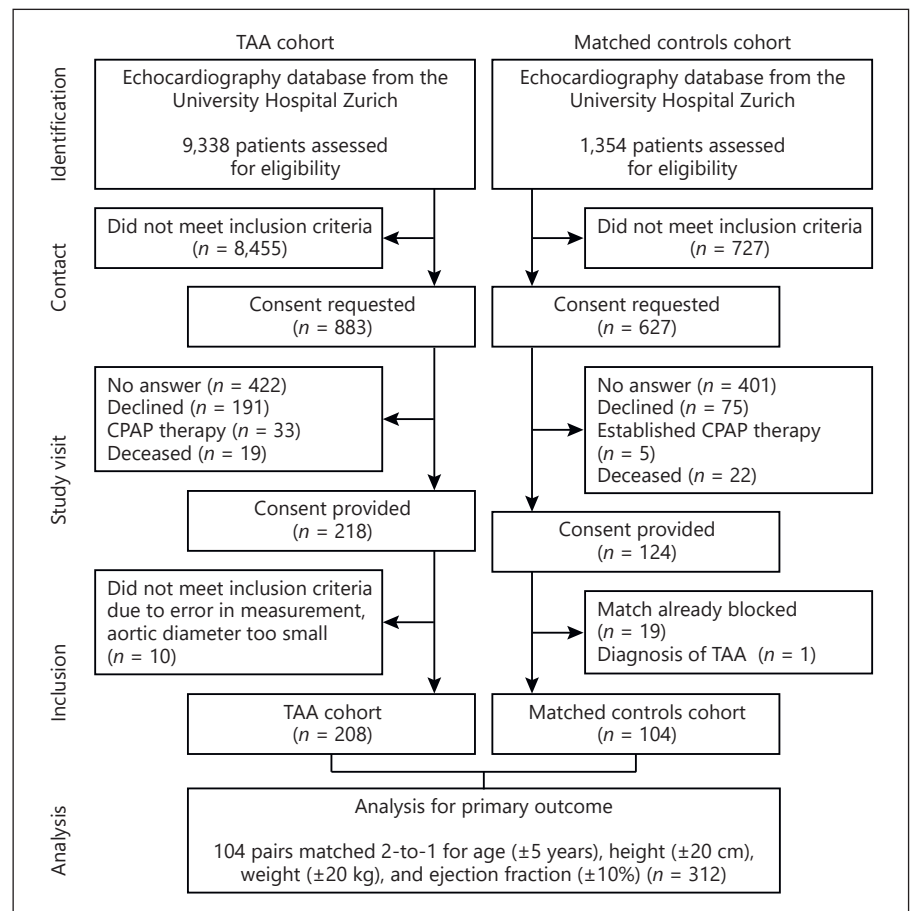


Fig. 1. Study flowchart.

Statistical Analysis

For the primary outcome, a sample size goal of >300 patients (200 cases, 100 controls) was established ($\alpha = 0.05$, $\beta = 0.2$) to detect an absolute difference in OSA of 10% between groups, assuming the prevalence rate of OSA in the TAA group is similar to those found in patients with abdominal aortic aneurysm [13]. As recommended, conditional logistic regression adjusted for the matching variables was used to compare the prevalence of OSA between groups [26]. We used a mixed effects regression analysis to compare continuous variables assessing OSA severity, adjusted for the matching variables and accounting for the cluster of each 2-to-1-matched pair as a random effect. A two-sided p value of <0.05 was considered statistically significant for all reported tests. Statistical analysis was performed with STATA Version 15 (StataCorp LP, College Station, TX, USA). Results are presented as mean (\pm standard deviation of the means) or median (interquartile range) as appropriate.

Results

Patient Characteristics

The matching process yielded 208 patients with TAA, 2-to-1 paired to 104 matched control subjects. The ini-

tially calculated sample size was surpassed by 4% ($n = 12$). The subjects were predominantly male (81.7%) and Caucasian (98%). The study flow chart is depicted in Figure 1. No statistically significant confounders were present for the matching variables. As expected, patients with TAA had a higher blood pressure (in terms of both, the pre-listed diagnoses and measurements performed in our study) and were significantly more often prescribed β -adrenoreceptor antagonists. For summary statistics and background information, see Tables 1 and 2. In patients with TAA, the aneurysm was present at the aortic sinus (32%) and the ascending aorta (25%) or both sites (43%) according to the prespecified values.

Primary Outcome

Sleep study data were available for all study participants, after 24 (TAA group) and 11 (control group) patients successfully repeated the testing due to initially insufficient data (<4 h of sleep or technical issues). The unadjusted median AHI (Fig. 2) was higher in patients with

Table 1. Summary statistics for patients with TAA and 2-to-1-matched controls

	TAA (n = 208)	Matched controls (n = 104)	p value
Anthropometrics			
Male sex, n (%)	170 (81.7)	85 (81.7)	–
Age, years	65.94±10.49	64.43±11.74	0.25
Height, cm	174.83±8.19	173.41±8.56	0.16
Weight, kg	82.12±13.01	80.81±12.11	0.39
BMI, kg/m ²	26.89±4.19	26.89±3.83	1.00
Neck circumference, cm ^a	39.26±3.28	39.83±3.87	0.17
Hip circumference, cm	99.96±11.81	102.08±7.54	0.10
Waist circumference, cm	102.16±9.23	99.96±12.72	0.09
Systolic blood pressure (office), mm Hg ^b	132.49±27.19	121.30±15.00	<0.01
Diastolic blood pressure (office), mm Hg ^b	81.86±11.78	77.71±9.78	<0.01
Heart rate (office), min ⁻¹	69.27±11.63	71.05±13.52	0.23
Comorbidities			
Smoker, n (%)	29 (14.1)	14 (13.5)	0.88
Pack years of smoking, pack years	17.99±25.57	14.90±20.74	0.30
Arterial hypertension, n (%)	155 (75.2)	51 (49.0)	<0.01
Dyslipidemia, n (%)	121 (59.6)	62 (59.6)	1.00
Diabetes mellitus type 2, n (%)	14 (7.2)	11 (10.8)	0.29
History of stroke, n (%)	30 (14.6)	11 (10.7)	0.34
History of coronary artery disease, n (%)	45 (22.0)	35 (34.0)	0.02
Abdominal aortic aneurysm, n (%)	10 (4.9)	2 (1.9)	0.21
Renal deficiency, n (%)	19 (9.2)	13 (12.6)	0.36
COPD, n (%)	15 (7.3)	3 (2.9)	0.12
Atrial fibrillation, n (%)	43 (20.9)	18 (17.5)	0.48
Marfan syndrome, n (%)	1 (0.5)	0 (0)	0.48
Turner syndrome, n (%)	0 (0)	0 (0)	–
Bicuspid valves, n (%)	14 (7.8)	1 (1)	0.01

COPD, chronic obstructive pulmonary disease; BMI, body mass index; TAA, thoracic aortic aneurysm.
^a Measured between the mid-cervical spine and the mid-anterior neck. ^b Office blood pressure: measured in triplicates and averaged by the mean.

TAA when compared to controls (9.2/h [3.3–20.0] vs. 4.5/h [2.2–11.1]; $p < 0.001$). In patients with TAA, OSA prevalence (defined as an AHI of ≥ 5 /h) was 63 versus 47% in the matched control group (odds ratio 1.87 [95% CI 1.05–3.34]; $p = 0.033$) adjusted for the matching variables age, sex, left ventricular ejection fraction, height, and weight. When applying a higher AHI threshold for OSA diagnosis (AHI ≥ 15 /h), the odds ratio increased to 3.25 (95% CI 1.65–6.42; $p < 0.001$). For the cut-off value of AHI ≥ 30 /h, however, this association was no longer statistically significant (OR 3.21, 95% CI 0.68–15.11, $p = 0.141$) primarily due to the decreased number of observations in this range. Unadjusted prevalence data are presented in Table 3. In the mixed effects model, age and weight were statistically significant direct predictors of a high AHI value (both

$p < 0.001$). Sex, height, and left ventricular ejection fraction were not associated with OSA severity ($p > 0.05$).

Secondary Outcome

The raw diameters (in cm) of the aortic sinus and the ascending aorta were associated with the raw AHI (events/h) in the TAA group (coefficient 6.5 [95% CI 1.3–11.8], $p = 0.01$ and coefficient 7.3 [95% CI 1.8–12.9] $p = 0.01$ respectively). However, further adjustments for all the matching variables (including an interaction term for weight and age) unmasked this association as insignificant ($p > 0.05$). This also applies to other variables from the sleep data (e.g., the oxygen desaturation index, the time spent below a peripheral oxygen saturation of 90%, mean peripheral oxygen saturation).

Table 2. Background information for patients with TAA and 2-to-1-matched controls

	TAA (n = 208)	Matched controls (n = 104)	p value
<i>Laboratory</i>			
Cholesterol, mmol/L	4.63±1.19	4.34±1.17	0.09
Triglycerides, mmol/L	1.59±0.82	1.78±1.69	0.24
High-density lipoprotein, mmol/L	1.40±0.50	2.53±9.64	0.13
Low-density lipoprotein, mmol/L	2.62±1.09	2.30±1.07	0.04
Diabetes mellitus type 2, n (%)	14 (7.2)	11 (10.8)	0.29
HbA _{1c} , %	5.65±0.64	5.68±1.11	0.83
<i>Medication</i>			
β-Adrenoreceptor antagonists, n (%)	107 (52.2)	38 (36.5)	<0.01
α-Adrenoreceptor antagonists, n (%)	11 (5.4)	6 (5.8)	0.88
Calcium channel blockers, n (%)	50 (24.5)	16 (15.4)	0.06
ACE inhibitors, n (%)	70 (34.1)	36 (34.6)	0.93
Angiotensin II receptor blocker, n (%)	51 (24.9)	17 (16.3)	0.09
Diuretics, n (%)	65 (31.7)	24 (23.3)	0.12
Aldosterone, n (%)	7 (3.4)	7 (6.7)	0.19
Total number of antihypertensives			<0.01
0 antihypertensive drugs, n (%)	36 (17.3)	36 (34.6)	
1 antihypertensive drug, n (%)	54 (26.0)	26 (25.0)	
2 antihypertensive drugs, n (%)	66 (31.7)	19 (18.3)	
3 antihypertensive drugs, n (%)	34 (16.3)	14 (13.5)	
4 antihypertensive drugs, n (%)	17 (8.2)	7 (6.7)	
5 antihypertensive drugs, n (%)	1 (0.5)	2 (1.9)	
Statins, n (%)	116 (56.6)	54 (51.9)	0.44
Oral antidiabetics, n (%)	10 (4.9)	7 (6.7)	0.50
Insulin, n (%)	3 (1.5)	2 (1.9)	0.76
Phenprocoumon, n (%)	50 (24.4)	11 (10.6)	<0.01
New oral anticoagulants, n (%)	14 (6.8)	12 (11.5)	0.16
Aspirin, n (%)	78 (38.0)	38 (36.5)	0.80
Dual antiplatelet therapy, n (%)	16 (7.8)	10 (9.6)	0.59
<i>Echocardiography</i>			
Left ventricular ejection fraction, %	57.54±8.50	55.68±10.19	0.10
Aortic sinus, cm	4.51±0.56	3.61±0.39	<0.01
Ascending aorta, cm	4.50±0.46	3.58±0.42	<0.01
Left ventricular myocardial mass index, g/m ²	100.5±32.1	80.19±24.18	<0.01
Left atrial end-systolic dimension, cm	4.00±0.82	3.94±0.75	0.58
Left ventricular end-systolic dimension, cm	3.2±0.7	3.19±0.84	0.69

ACE, angiotensin-converting-enzyme; HbA_{1c}, glycated hemoglobin; TAA, thoracic aortic aneurysm.

Other Variables

In our study, the systolic and diastolic office blood pressure was not associated with the AHI (events/h) (coefficient 0.02 [95% CI −0.03 to 0.08], $p = 0.44$, and coefficient 0.10 [95% CI −0.30 to 0.24], $p = 0.12$, respectively) and neither was the diagnosis of arterial hypertension (coefficient 2.4 [95% CI −0.78 to 5.55], $p = 0.14$). Also, no significant association between the AHI and low-density lipoprotein could be established (data not shown).

Discussion

To our knowledge, this is the first study to report a higher prevalence of OSA in patients with TAA when compared to a matched control group. We found an approximately 1.3-fold increased prevalence of OSA in patients with TAA when compared to a matched control group.

Sixty-three percent of patients with TAA had an AHI of ≥ 5 /h, which was in line with previously published

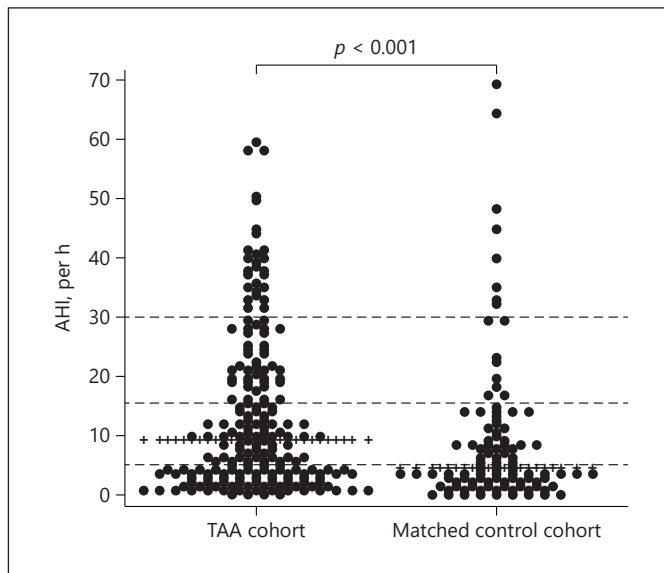


Fig. 2. Apnea-hypopnea index (AHI) by groups. Conventional thresholds for the AHI (5, 15, and 30) are marked with a dashed line. The median of each group is indicated with the black bar. The median AHI was higher in patients with TAA (9.2/h [3.3–20.0] vs. 4.5/h [2.2–11.1]).

prevalence data on OSA among patients with an abdominal aortic aneurysm [13]. Compared to the study of Mason et al. [13], which investigated an anthropometrically similar population with abdominal aortic aneurysms (68 ± 6 years old, BMI 28 ± 4 kg/m², 91% male, $n = 127$), we report almost identical results regarding the AHI (mean 13.8 ± 16.6 vs. 13.6 ± 13.4 and prevalence of 64 vs. 63% in our study). On the other hand, the prevalence of OSA among patients with TAA in our study tends to be lower than the rates from the five previously described cohorts encompassing patients after aortic dissections, ranging from 61 to 82% [15–18, 20]. Still, to our knowledge, our TAA sample represents the largest cohort studied so far in aortic disease [13, 15–18, 20]. Most importantly, all studies investigating the impact of OSA on the aorta which included a control-group, reported a higher prevalence of OSA in the aortic disease group [14, 16, 17, 20]. Our study confirms this relationship for patients with TAA and adds further evidence to the association between OSA and aortic disease. Our study delivers further support to the association between OSA and aortic disease in general. So far, six cross-sectional cohorts have described an association between the severity of OSA and the diameter of the aorta [10, 27–31]. Although we included this association as a secondary outcome in our study, we were not able to reproduce these previous find-

ings after adjusting for age, weight, sex, and left ventricular ejection fraction. Severe OSA was not independently associated with a greater aortic diameter. This result was, however, in line with two other studies on this topic, which also accounted for the same confounders [32, 33].

The underlying mechanisms by which OSA might contribute to aortic disease are currently subject to investigation [6]. We identified three studies, describing distensions of the thoracic aorta during simulated obstructive apneas, leading to additional dilatory force measured via an aortic catheter [34–36]. Another study measured the nocturnal negative intrathoracic pressure surges in patients with untreated OSA; these could reportedly peak up to -147 cm H₂O [37]. It is plausible to assume that such repetitive, negative pressure surges promote a long-term distension of the aorta [6]. Additionally, the prolonged sympathetic activation with subsequent blood pressure elevation in patients with OSA may also play a crucial role. In OSA, arterial blood pressure is particularly elevated during sleep, and nocturnal non-dipping patterns (diminished night-time blood pressure reductions) are especially prominent [38]. Meta-analyses have also consistently demonstrated the long-term blood pressure rises in OSA, and arterial hypertension is one of the main risk factors associated with the incidence of TAA [2, 7]. Finally, it is also plausible that OSA-induced overall increase in oxidative stress (e.g., in the endothelium) further contributes to aortic remodeling [6].

As expected, patients with TAA displayed a significantly higher prevalence of bicuspid aortic valves and a higher left ventricular myocardial mass index in our cohort. This is in line with previous population-based studies, where bicuspid valves are a risk factor for TAA [39]. In addition, untreated OSA over a long period is associated with the development of left ventricular hypertrophy [40]. However, in our study, we could not find a statistically significant association in a post hoc analysis between AHI/ODI, systolic/diastolic blood pressure versus the left ventricular myocardial mass index or the bicuspid valves vs. the AHI, respectively (data not shown). Thus, it is unlikely that these parameters might have influenced our primary outcome. It is important to note that the presence of arterial hypertension can also contribute to the increase in TAA and left ventricular myocardial mass index, respectively, and therefore might possibly explain the differences in Table 1 irrespective of the presence of OSA [41].

Table 3. Sleep study data for the study population

	TAA (<i>n</i> = 208)	Matched controls (<i>n</i> = 104)	<i>p</i> value
Apnea hypopnea index, h ⁻¹	9.2 (3.3–20.0)	4.5 (2.2–11.1)	<0.01
Apnea hypopnea index ≥5 h ⁻¹	131 (63%)	49 (47%)	<0.01
Apnea hypopnea index ≥15 h ⁻¹	71 (34%)	16 (15%)	<0.01
Apnea hypopnea index ≥30 h ⁻¹	27 (13%)	8 (8%)	0.16
Oxygen desaturation index (4%), h ⁻¹	13.52±12.65	9.04±12.72	<0.01
Total time in bed, h	6.32±1.51	6.42±1.70	0.82
Respiratory rate, min ⁻¹	14.78±2.58	14.23±2.92	0.09
Epworth Sleepiness Scale, points	6.29±3.88	6.82±3.67	0.25

Sleep data were derived from one night with level III respiratory polygraphy and scored according to the American Society of Sleep Medicine criteria from 2007 (version A) [23]. Data are reported as mean (SD) or median (25th–75th percentiles) as appropriate. TAA, thoracic aortic aneurysm.

Limitations

One limitation of our study was the fact that we used level III respiratory polygraphy in a single overnight study to measure OSA severity, rather than the gold standard polysomnography. However, a level III respiratory polygraphy demonstrated a good overall agreement with polysomnography in terms of AHI and oxygen desaturation indices and was therefore proven to be non-inferior in the clinical setting [42]. Furthermore, we did not perform a 24-h ambulatory blood pressure monitoring, which would be more precise [25], and the limitations of ultrasound did not allow for inclusion of TAA at the aortic arch and descending aorta, which represent approximately 50% of all TAA [40]. The high proportion of males in our study may be regarded as a limitation when it comes to the generalizability of the data. Finally, it is noted that our design of the study does not allow establishing any causal relationships between OSA and TAA.

Conclusions

The prevalence of OSA is higher among patients with TAA than in the general population. Since OSA is effectively treatable and might contribute to the pathogenesis of TAA in several ways, further longitudinal studies assessing the relationship between the two are necessary. In the future, this might result in recommendations of screening for OSA among patients suffering from specific subtypes of aortic diseases.

Acknowledgements

We want to thank all the participants and their relatives who often travelled long distances to be part of our project. This study would not have been possible without their commitment.

Statement of Ethics

The study was approved by the Cantonal Ethics Committee Zurich, Switzerland (KEK-ZH-Nr. 2014-0035), and all participants provided written informed consent prior to participation. The primary outcome and the study itself were registered a priori (ClinicalTrials.gov Identifier: NCT03400319). The data that support the findings of this study are available from the corresponding author upon reasonable request.

Disclosure Statement

T.G. and M.K. report consulting fees from Bayer AG, outside the submitted work. All other authors report no conflicts of interest.

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Author Contributions

T.G. and P.B. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: T.G., M.K. Acquisi-

tion, analysis, or interpretation of data: T.G., P.B., P.R., M.R., S.T., S.F.S., M.O. Drafting of the manuscript: T.G., P.B. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: T.G., P.B. Administrative, technical, or material support: T.G., C.F.C., F.C.T., M.K. Study supervision: M.K.

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